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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/472,691	12/27/1999	TERRY HERMISTON	ONYX1022	9088

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/472,691	Applicant(s) HERMISTON ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 1-15 are pending examination.

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be to directed to Brian Whiteman, Art Unit 1635.

Continued Prosecution Application

The request filed on 6/3/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/472,691 is acceptable and a CPA has been established. An action on the CPA follows.

Drawings

NOTE: In the next response, please submit a response to the PTO 498 because a PTO 498 is filed with this non-final rejection. If the reply to the Non-Final Rejection does not have a response to the 498, the response will be considered non-responsive. See 37 CFR 1.85(a).

Claim Objections

Claim 11 is objected to because of the following informalities: improper grammatical phrase "a chemotherapeutic or an immunosuppressive". Suggest adding the term "agent" or "regimen" after the word "immunosuppressive". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A method for reducing tumor burden in a mammal comprising directly administering to a tumor a therapeutically effective dose of an adenoviral vector comprising a deletion of E1B region, but retaining the E1B promoter and substituting for E1B region an anti-tumor gene, and does not reasonably provide enablement for the full scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

This invention encompasses to the production of adenovirus E1B shuttle vectors and methods for making and using such vector (e.g. treating neoplastic condition in a mammal). The invention lies in field of the gene therapy.

Furthermore, and with respect to claims directed to any vector useful for gene therapy and directed to any treatment of a mammal; the state of the art in 1998, exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

The specification teaches production of an adenovirus vector containing a mutation in the E1b region (pages 21-24). In addition the as-filed specification teaches insertion of a transgene (e.g. cytosine deasminase (CD), TNF) into the shuttle vector (pages 24-27).

In view of the In re Wands Factors, the as-filed specification teaches one skilled in the art how to make and/or use a recombinant adenovirus vector comprising a deletion of E1B region but retaining the E1B promoter in a method of reducing tumor burden comprising directly administering the adenovirus vectors to the tumor. However, the breadth of the term "treating", which reads on a full therapeutic response of any neoplastic condition (e.g. complete regression of a neoplastic condition) and the term "neoplastic condition" read on a broad range of neoplastic conditions (including localized or metastatic tumor, hyperproliferative disorders, etc.) and in view of the art of record and the breadth of the terms, the as-filed specification lacks sufficient guidance for one skilled in the art to use the adenovirus vectors taught in the disclosure for full breadth of the claims, which encompasses treating a mammal having any neoplastic condition. In addition, in view of the art of record, it is not apparent to one skilled in the art how to use any heterologous gene other than anti-tumor genes in a method of treating a mammal having a tumor. Furthermore, the breadth of the term "heterologous gene" reads on a broad range of genes, including dystrophin, Factor VIII, CD, thymidine kinase, etc. In view of the breadth of the term, the as-filed specification lacks sufficient guidance for one skilled in the art to use the adenovirus vectors taught in the disclosure comprising any heterologous gene other than anti-tumor gene for treating a mammal having a tumor.

Furthermore, in further view of the doubts expressed above by Anderson and Verma, the state of the art at the time the application was filed and currently for cancer gene therapy as discussed by Vile et al., (*Gene Therapy*, Vol. 7, pp. 2-8, 2000). Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. None the less, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).

Vile further discusses:

> A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor

from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

Thus, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) other than direct administration to the neoplastic cells would result in a therapeutic response in a mammal having a neoplastic condition using the recombinant adenoviral vector set forth in the claimed invention. The state of the art for the route of administration for gene therapy as exemplified by Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Furthermore, the as-filed specification only displays the production of E1B deleted shuttle adenoviral vectors and the expression of a transgene in vitro. The state of art further displays intravenously (i.v.) administering ONYX-15 to a research model, (immunodeficient mice with a subcutaneous human xenograft tumor) and observing a decrease in tumor growth (Bischoff et al., US Patent No. 6,080,578, columns 22-23). However, in view of the art of record (for example see Mastrangelo et al., Seminars in Oncology, Vol. 23, 1996, pp. 4-21), the research murine model does not reasonably extrapolate to treating neoplastic cells in a mammal using any route of administration other than direct administration using the claimed adenoviral vector. In addition, in view of the art of record teaching the unpredictability of systemically administering any vector for treating cancer in a mammal and the lack of guidance provided by the as-filed

specification for how to overcome the problems with any route of administration other than direct administration, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from direct administration to any other route of administration for treating neoplastic cells in a mammal using the claimed invention. Therefore, in view of the state of the art, it is not apparent to one skilled in the art how to reasonably extrapolate from direct administration to neoplastic cells to any other route of administration to generate a therapeutic response in any mammal having a neoplastic condition. As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed adenovirus generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the for 1 listed above. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition (e.g. neoplastic condition) in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any gene delivery vector cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

To the extent that the applicants' traversal (See paper no. 12. pages 3-4) is applicable to the rejection under 112 enablement, the traversal is not found partially persuasive for 1 listed.

However, in view of the art of record, the as-filed specification and the applicants' traversal fail to provide sufficient guidance and/or factual evidence for how direct administration of said adenovirus vector to said neoplastic cells reasonably correlates to any other route of administration for delivering said vector to said cells. In addition, the applicants' traversal and/or the as-filed specification fail to provide sufficient guidance and/or factual evidence for how to use any heterologous gene other than anti-neoplastic genes for treating neoplastic cells in a mammal having a neoplastic condition.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2, 3, 4, 5, 6, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The statement in claims 2-6, "**An** (recombinant) adenoviral vector as described in claim 2 (1 or 15)" is indefinite because it does not point out which composition **an** adenoviral is referring to in the claim. Claim 1 or 15 each encompass one adenoviral vector and claims 2-6 refer to several adenoviral vectors. The dependent claim should state "**The** adenoviral vector as described in claim 2".

To the extent that applicants' traversal is applicable to the new rejections under 112 second paragraph, the traversal is not found persuasive because they are not applicable to the rejections set forth above.

The statement in claim 11, "**A** method as described in claim 10...." is indefinite because it does not point out which method **a** method is referring to in the claim. The dependent claim should state "**The** method as described in claim 10...".

To the extent that applicants' traversal is applicable to the new rejections under 112 second paragraph, the traversal is not found persuasive because they are not applicable to the rejections set forth above.

Claims 3-5 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: how the active step "deleting" comprises p19, 55k, and pIX. The claims do not particularly define or point out how p19, 55k, and pIX can be used in a deletions step. Suggest amending the claims to read as follows: The adenoviral vector described in claim 2, wherein the E1B gene deletion comprises the pIX gene.

To the extent that applicants' traversal is applicable to the new rejections under 112 second paragraph, the traversal is not found persuasive because they are not applicable to the rejections set forth above.

Claim Rejections - 35 USC § 102

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined

was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-3, 6-7, 9-11, and 14-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Bischoff (US Patent No. 6,080,578). Bischoff teaches mutant viruses with a replication competent phenotype in neoplastic cells (abstract). Bischoff further teaches that the preferential killing of the neoplastic cells resulted either directly or by the expression of a cytotoxic gene in cells (abstract). Furthermore, Bischoff teaches recombinant adenovirus constructs comprise a mutation in the E1a and/or E1b 55 protein (column 4, lines 32-54). A gene is operably linked to an early region (e.g. E2, E1a, E1b) enhancer/promoter, or an early gene promoter. In addition, Bischoff also taught the construction of plasmids comprising several E1B deletions and deposited at the ATCC depository (column 11, line 24- column 14, line 18, claims 4-6, and columns 25 and 26). Bischoff also teaches the efficacy of ONYX-015 (note that ONYX-015 does not make detectable 55kD) alone and in combination with chemotherapy in a research tumor animal model (column 22, line 55 - column 23).

Applicants traverse the rejection under 102(e) because Bischoff does show recombinant adenoviruses comprising an E1B deletion and that such virus can be used for killing cancer. However, nowhere in Bischoff is there a showing of deleting a gene or genes from E1B region of adenovirus, inserting a heterologous gene, and having a gene operably linked to the E1B promoter. (See page 5 of paper no. 12).

Applicants' traversal is acknowledged and is not found persuasive for the following reasons: Bischoff teaches the construction of plasmids comprising several E1B deletions and

deposited at the ATCC depository (column 11, line 24- column14, line 17, claims 4-6, and columns 25 and 26). More specifically, Bischoff teaches the production of E1b mutants included a mutation in the p19 and/or 55K protein (column 11, line 22- column 14, lines 18), while retaining the E1b promoter operably linked to a negative selective gene (thymidine kinase).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bischoff (US Patent No. 6,080,578) taken with Garcia-Sanchez et al (Blood, Vol. 92, 1998, pp. 672-682). Bischoff teaches mutant viruses with a replication competent phenotype in neoplastic cells (abstract). Bischoff further teaches that the preferential killing of the neoplastic cells resulted either directly or by the expression of a cytotoxic gene in cells (abstract). Furthermore, Bischoff teaches recombinant adenovirus constructs comprise a mutation in the E1a and/or E1b 55 protein (column 4, lines 32-54). A gene is operably linked to an early region (e.g. E2, E1a, E1b) enhancer/promoter, or an early gene promoter. In addition, Bischoff also taught the construction of plasmids comprising several E1B deletions and deposited at the ATCC depository (column 11, line 24- column 14, line 18, claims 4-6, and columns 25 and 26). Bischoff also teaches the efficacy of ONYX-015 (note that ONYX-015 does not make detectable 55kD) alone and in combination with chemotherapy in a research tumor animal model (column 22, line 55 - column 23). However, Bischoff does not specifically the production of a recombinant adenovirus vector comprising a deletion of E1b region gene, but retaining the E1b promoter, and substituting for said deleted E1b region gene, an anti-tumor gene, wherein the gene is cytosine deaminase (CD).

However, at the time the invention was made, Garcia Sanchez teaches production of adenoviral vector comprising a cytosine deaminase (CD) used for killing cancer cells (abstract). CD converts the antibiotic pro-drug 5-fluorocytosine into the cytotoxic chemotherapeutic agent 5-fluorouracil.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to insert a CD gene instead of thymidine kinase gene into the

recombinant adenoviral vector taught by Bischoff. One of ordinary skill in the art would have been motivated to insert any anti-tumor gene product (e.g. CD) in the recombinant adenoviral vector because Bischoff teaches that any cytotoxic gene could be use to treat tumor cells in a mammal.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

To the extent that the applicants traverse is applicable to the rejection under 103(a). The traversal is acknowledged and is not found persuasive for the following reasons: Bischoff teaches the construction of plasmids comprising several E1B deletions and deposited at the ATCC depository (column 11, line 24- column14, line 17, claims 4-6, and columns 25 and 26). More specifically, Bischoff teaches the production of E1b mutants included a mutation in the p19 and/or 55K protein (column 11, line 22- column 14, lines 18), while retaining the E1b promoter operably linked to a negative selective gene (thymidine kinase).

Claims 1, 2, 4, 7, 14, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bischoff (US Patent No. 6,080,578) taken with Amalfitano et al. (US Patent No. 6,328,958, effective filing date 8/28/98). Bischoff teaches mutant viruses with a replication competent phenotype in neoplastic cells (abstract). Bischoff further teaches that the preferential killing of the neoplastic cells resulted either directly or by the expression of a cytotoxic gene in cells (abstract). Furthermore, Bischoff teaches recombinant adenovirus constructs comprise a mutation in the E1a and/or E1b 55 protein (column 4, lines 32-54). A gene is operably linked to an early region (e.g. E2, E1a, E1b) enhancer/promoter, or an early gene promoter. In addition, Bischoff also taught the construction of plasmids comprising several E1B deletions and

deposited at the ATCC depository (column 11, line 24- column 14, line 18, claims 4-6, and columns 25 and 26). However, Bischoff does not specifically the production of a recombinant adenovirus vector comprising a deletion of E1b region gene, but retaining the E1b promoter, wherein the E1B gene deletion comprises pIX and substituting for said deleted E1b region gene, an anti-neoplastic gene.

However, at the time the invention was made, Amalfitano teaches that first-generation adenovirus vectors are typically deleted for the E1 genes and packaged using a cell that expresses the E1 proteins (e.g., 293 cells) (column 10, lines 33-60). The E3 region is also frequently deleted as well, as there is no need for complementation of this deletion. In addition, deletions in the E4, E2a, protein IX, and fiber protein regions have been described. The deletions are selected to avoid toxicity to the packaging cell. Amalfitano further teaches that combinations of deletions that avoid toxicity or other deleterious effects on the host cell can by routinely selected by those skilled in the art.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the recombinant adenoviral vector taught by Bischoff by deleting the pIX gene. One of ordinary skill in the art would have been motivated to modify the adenoviral vector by deleting the pIX gene region to further avoid toxicity to the packaging cells and because it was in the skill of one of ordinary skill in the art to routinely delete gene regions (e.g. pIX gene region) from a recombinant adenoviral vector.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

To the extent that the applicants traverse is applicable to the rejection under 103(a). The traversal is acknowledged and is not found moot for the reasons set forth above.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

Brian Whiteman
Patent Examiner, Group 1635
8/26/02